Claim 8, line 1, delete "or 2".

Claim 15, line 1, delete "or 2".

17. (Twice Amended) The process according to claim 1 [or 2], wherein the microorganism capable of producing a sugar nucleotide from a sugar and NTP comprises at least one [kind of] microorganism.

REMARKS

Claim 1 has been amended in order to recite the present invention with the specificity required by statute. Additionally, Claims 5, 8, 15 and 17 have been amended for better conformity with accepted U.S. practice and/or to better depend from their antecedent claims. Claims 2-4, 6, 7, 9-14 and 21-71 are cancelled in order to reduce the issues. Accordingly, no new matter has been added.

Claim 1 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that it is not clear from the specification

what the term "treated product" means. In response, Applicants respectfully wish to invite the Examiner's attention to the text from specification page 36, line 14 to page 37, line 2.

Claim 17 also is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response, claim 17 has been amended in conformity with the Examiner's kind suggestion.

Claim 1 is also rejected under 35 U.S.C. §112, first paragraph, as failing to be supported by an enabling disclosure. In particular, the Examiner notes that the specification enables production of uridine phosphogalactose but contends does not teach those of ordinary skill how to make other sugar nucleotides without undue experimentation.

As the Examiner is aware, the present invention relates to a process for producing a sugar nucleotide using "a microorganism capable of producing NTP from an NTP precursor", and "a microorganism (or recombinant) having genes responsible for production of a sugar nucleotide from a sugar and NTP."

The "microorganism" capable of producing NTP from an NTP precursor includes microorganisms described at page 12, lines 5-15 in the present specification. In the description, as the microorganism suitable for producing NTP from an NTP precursor, exemplified are *Escherichia coli* [*Escherichia coli and Salomonella, Cellular and Molecular Biology*, second edition, pages 573 and 582 (1996)] in which the NTP biosynthetic pathway is known, and *Corynebacterium ammoniagenes* (EP 0 553 821 A1) which is reported to be have a high productivity of UTP from orotic acid. However, as is apparent that NTP is a component constituting a nucleic acid, it is an essential element in the survival of microorganisms so that it is clear that any microorganism has a capability of producing NTP. Also, since the NTP biosynthetic pathway is a main metabolic pathway, similar to saccharometabolism pathway and TCA cycle, the difference in the NTP biosynthetic pathway between microorganisms would be little. Accordingly, any microorganism would have the capability of producing NTP from an NTP precursor which is similar to the NTP precursor known in the above *E. coli* and *C. ammoniagenes*, i.e.,

* GTP precursors, such as guanine, guanosine, GMP, IMP, inosine, XMP, xanthosine, xanthine, and hypoxanthine;

* UTP precursors, such as orotate, OMP, UMP, uridine, and uracil; and

* CTP precursos, such as orotate, OMP, UMP, uridine, uracil, cytidine, CMP, and cytosine.

Those of ordinary skill in the art would select a precursor from the above precursors and further select a microorganism capable of producing NTP from the precursor without undue experimentation.

Also, there are many microorganisms of which sugar chain structure present in the cell surface layer is clarified in literature [*Adv. Microbiol. Physiol.*, *35*: 135-246 (1993)]. Such are plainly capable producing a sugar nucleotide corresponding to a sugar in the sugar chain.

Additionally, DNAs derived from an enzyme relating to a pathway in which a sugar nucleotide is biosynthesized from a sugar and NTP (and a microorganism encoding the enzyme) are exemplified at page 12, line 20 to page 28, Table 2. Such are well known in various sugar nucleotides other than uridine diphosphogalactose. As disclosed in the present specification, specific examples include:

(1) Examples of an enzyme relating to a step of producing UDP-glucose from NTP and a sugar, and a gene encoding the enzyme include:

* glucokinase, and glk gene encoding glucokinase [*J. Bacteriol.*, *179*: 1298 (1997)],

* hexokinase, and a gene encoding hexokinase,

* glucose-1-phosphate uridyltransferase, and galU gene encoding glucose-1-phosphate uridyltransferase [*J. Biochem.*, *115*: 965 (1994)], and

* pyrophosphatase, and ppa gene encoding pyrophosphatase [*J. Bacteriol.*, *170*: 5901 (1988)].

(2) Examples of an enzyme relating to a step of producing UDP-galactose from NTP and a sugar, and a gene encoding the enzyme include:

* galactokinase, and galK gene encoding galactokinase [*Nucleic Acid Res.*, *13*: 1841 (1985)], and

* galactose-1-phosphate uridyltransferase, and galT gene encoding galactose-1-phosphate uridyltransferase [*Nucleic Acid Res.*, *14*: 7705 (1986)].

(3) Examples of an enzyme relating a step of producing UDP-N-acetylglucosamine from NTP and a sugar, and a gene encoding the enzyme include:

* glucokinase, and glk gene encoding glucokinase [*J. Bacteriol.*, *179*: 1298 (1997)],

* hexokinase, and a gene encoding a hexokinase,

* phosphoglucosamine mutase, and glmM gene encoding phosphoglucosamine mutase [*J. Biol. Chem.*, *271*: 32 (1996)],

* glucosamine-1-phosphate acetyltransferase, and glmU gene encoding glucosamine-1-phosphate acetyltransferase [*J. Bacteriol.*, *175*: 6150 (1993)],

* N-acetylglucosamine-1-phosphate uridyltransfearse, and glmU gene encoding N-acetylglucosamine-1-phosphate uridyltransfearse [*J. Bacteriol*, *175*: 6150 (1993)],

* phosphofructokinase, and pfkB gene encoding phosphofructokinase [*Gene*, *28*: 337 (1984)],

* phosphoglucomutase, and pgm gene encoding phosphoglucomutase [*J. Bacteriol.*, *176*: 5847 (1994)], and

* galactokinase, and galK gene encoding galactokinase [*Nucleic Acid Res.*, *13*: 1841 (1985)].

(4) Examples of an enzyme relating to a step of producing UDP-N-actylgalactosamine from NTP and a sugar, and a gene relating to the enzyme include:

* the above-described enzyme relating to a step of producing UDP-N-acetylglucosamine from NTP and a sugar, and a gene encoding the enzyme, and

* UDP-GlcNAc 4-epimerase, and a gene encoding the enzyme.

(5) Examples of an enzyme relating to a step of producing UDP-glucronic acid from NTP and a sugar, and a gene encoding the enzyme include:

* the above enzyme relating to a step of producing UDP-glucose from NTP and a sugar, and a gene encoding the enzyme, and

* UDP-glucose dehydrogenase and udg gene encoding UDP-glucose dehydrogenase [*J. Bacteriol.*, *177*: 4562 (1995)].

(6) Examples of an enzyme relating to a step of producing GDP-mannose and NTP and a sugar, and a gene encoding the enzyme include:

* glucokinase, and glk gene encoding glucokinase [*J. Bacteriol.*, *179*: 1298 (1997)],

* hexokinase, and a gene encoding hexokinase,

* phosphomannomutase, and manB gene encoding phosphomannomutase [*J. Bacteriol.*, *178*: 4885 (1996)], and

* mannose-1-phosphate guanyltransferase, and manC gene encoding mannose-1-phosphate guanyltransferase [*J. Bacteriol.*, *178*: 4885 (1996)].

(7) Examples of an enzyme relating to a step of producing GDP-fucose from NTP and a sugar, and a gene encoding the enzyme include:

* an enzyme relating to a step of producing GDP-fucose form NTP and a sugar, and a gene encoding the enzyme,

* an enzyme relating to a step of producing GDP-mannose form NTP and a sugar, and a gene encoding the enzyme,

* GDP-mannose-4,6-dehydratase, and gmd gene encoding GDP-mannose-4,6-dehydratase [*J. Bacteriol.*, *178*: 4885 (1996)], and

* GDP-4-keto-6-deoxymannose epimerase/reductase, and wcaG gene encoding GDP-4-keto-6-deoxymannose epimerase/reductase [*J. Bacteriol.*, *178*: 4885 (1996)].

(8) Examples of an enzyme relating to a step of producing CMP-N-acetylneuraminic acid from NTP and a sugar, and a gene encoding the enzyme include:

* N-acetylglucosamine 2-epimerase, and a gene encoding N-acetylglucosamine 2-epimerase,

* N-acetylneuraminic acid aldolase, and nanA gene encoding N-acetylneuraminic acid aldolase [*Nucleic Acid* res., *13*: 8843 (1985)],

* N-acetylneuraminic acid synthase, and neuB gene encoding CMP-N-acetylneuraminic acid synthase [*J. Bacteriol.*, *177*: 312 (1995)],

* CMP-N-acetylneuraminic acid synthetase, and neuA gene encoding CMP-N-acetylneuraminic acid synthetase [*J. Biol. Chem.*, *264*: 14769 (1989)], and

* CTP synthase, and pyrG gene encoding CTP synthase [*J. Biol. Chem.*, *261*: 5568 (1986)].

Accordingly, it is in fact unclear what is not taught in the present spcification.

That is, based on the teachings herein, one of ordinary skill would readily select the production process without undue experimentation.

Specifically, if the target sugar nucleotide is selected, the kind of NTP necessary for conducting the process of claim 1 is decided, and the microorganism capable

of producing NTP from the NTP precursor too can be selected. Also, one of ordinary skill in the art would obtain and select a microorganism having genes relating to the production of a sugar nucleotide from NTP and a sugar without undue experimentation.

One of ordinary skill in the art would obtain the culture broth of the above obtained and selected microorganism from the method described at page 33, line 13 to page 36, line 8. Moreover, the reaction conditions for producing a sugar nucleotide using the above "culture broth" and "treated product of the culture broth" are disclosed at page 37, line 3 to page 40, line 18.

Claim 1, 5, 8 and 15-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Maruyama et al. (EP 0 553 821 B1, dated 3-19-97) in view of Weissborn et al. (J. Bacteriol. 1994, Vol. 176:2611-2618). Please let us know how you wish us to distinguish the present invention from the Examiner's combination of prior art.

Maruyama discloses a process for producing UTP using orotic acid as a UTP precursor, and *C. ammoniagenes*. Weissborn confirms that UDP-glucose is produced using a cell

extract containing the galU gene product of *E. coli* from UTP and glucose 1-phosphate.

On the other hand, the present invention relates to a process for producing a sugar nucleotide from NTP and a sugar using a culture broth or treated product of the culture broth of a microorganism capable of producing NTP from an NTP precursor, and a culture broth or a treated product of the culture broth of a microorganism (or recombinant) having genes relating to the production of a sugar nucleotide form NTP and a sugar.

Maruyama neither discloses nor suggests producing a sugar nucleotide from NTP and a sugar. Also, according to Weissborn, UDP-glucose is produced under the optimum reaction conditions of the galU gene product, using labeled glucose 1-phosphate which is a substrate thereof. However, Weissborn neither discloses nor suggests that UDP-glucose can be produced from glucose via glucose 1-phosphate, i.e., a process for producing UDP-glucose using glucose as a substrate. In the process of Weissborn, UDP-glucose cannot be detected without using a labeled substrate in the enzyme reaction producing UDP-glucose from glucose 1-phosphate because a production amount of UDP-glucose is only a little

Accordingly, even if UDP-glucose is produced using glucose as a substrate via glucose-1-phosphate, the production amount would be further decreased.

In contrast, the present invention shows that various sugar nucleotides can be produced from substrates of NTP and a sugar, using a culture broth or treated product of the culture broth of a microorganism capable of producing NTP from an NTP precursor, and a culture broth or a treated product of the culture broth of a microorganism (or recombinant) having genes relating to the production of a sugar nucleotide form NTP and a sugar (Examples 2, 4, 6, 9, 12, 14, 16 and 18). The production amounts thereof are several grams to several ten grams per liter, so that markedly high productivity can be obtained. Also, the present invention is economically more excellent than Weissborn because the present invention uses, as a substrate, a very inexpensive sugar, such as glucose, in comparison with glucose 1-phosphate used in Weissborn.

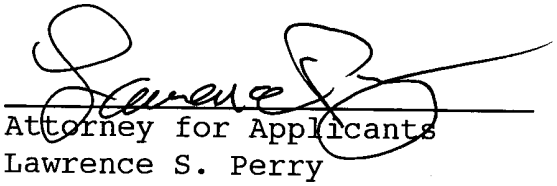
In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition.

Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 1, 5, 8 and 15-20 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should be directed to our below listed address.

Respectfully submitted,



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